REMARKS

Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC § 103.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejects claims 1-14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jacobs et al., *Stroke* (1999) in view of page 1562 of Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th Ed.). Specifically, the Examiner states

> Therefore, in view of the combined teachings of the cited references, one skilled in the neurology art would have been motivated to administer one of the forms of vitamin B_6 to treat ischemic stroke. Such would have been obvious because Jacobs teaches a deficiency in the vitamin to be a finding that is highly correlated to a high risk of ischemic stroke. The administration of B_6 will provide pyridoxal 5'-phosphate to the systemic circulation after metabolism in the liver. Office Action, May 11, 2007 at p. 3.

Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, the prior art reference(s) must disclose or suggest all the claim limitations. MPEP § 2143; *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Although the traditional analysis of obviousness has been modified under *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), the Supreme Court still holds that a case of obviousness under 35 U.S.C. § 103(a) still requires the disclosure or suggestion of all claim elements. Applicants respectfully assert that the cited art does not teach or suggest all the claim limitations or provide a reasonable expectation of success. Pyridoxine is distinct from pyridoxal-5'-phosphate. Administration of a therapeutically effective amount pyridoxine has been both toxic and ineffective in treating cardiovascular pathologies. Applicants teach administering a therapeutic amount of pyridoxal-5'-phosphate and not a nutritionally sufficient amount. Applicants respectfully assert that the Examiner has not sufficiently established a *prima facie* case of obviousness.

Cited Art. The Examiner cites Jacobs et al., *Stroke* (1999) as reciting an association between decreased levels of vitamin B_6 and an increased risk of ischemic stroke. To be more specific, Jacobs et al. evaluated the relationship of ischemic stroke with the dietary intake of vitamin B_6. Jacobs et al. do not provide support for using pyridoxal-5'-phosphate (P5P) since

vitamin B_6 (pyridoxine) is pharmaceutically distinct from pyridoxal-5'-phosphate (discussed below in further detail). Additionally, Jacobs et al. only look at nutritional levels via dietary intake and not a therapeutically effective amount of pyridoxal-5'-phosphate delivered as a pharmeutical (discussed below in further detail). The Examiner also cites a general pharmacological textbook, Goodman & Gilman's for disclosing pyridoxine and pyridoxal-5'-phosphate. Applicants respectfully assert that the cited art does not support a method of treating cerebral ischemia or ischemic stroke by administering a therapeutically effective amount of pyridoxal-5'-phosphate.

Pharmaceutically Distinct. Although there are metabolic pathways from all of the vitamin B_6 precursors to pyridoxal-5'-phosphate, they are not pharmaceutically equivalent. These differences apply to safety, pharmacodynamics, pharmacokinetics and bioavailability. For instance, published reports indicate that doses of pyridoxine over 25 mg produce little change in plasma pyridoxal-5'-phosphate levels (Ubbink *et al*, 1987). Thus it is impossible that therapeutic plasma levels of pyridoxal-5'-phosphate could be obtained through oral pyridoxine supplementation. In terms of pharmacodynamics, pyridoxal-5'-phosphate is likewise differentiated from vitamin B_6. For example, *in vitro* experiments comparing the antioxidant activity of different B_6 derivatives demonstrated that pyridoxal-5'-phosphate had significantly greater antioxidant activity than did pyridoxine (Chumnantana *et al*, 2005). Similarly, *in vitro* experiments comparing the ability of different B_6 derivatives to prevent lipid peroxidation demonstrated that pyridoxal-5'-phosphate significantly reduced lipid peroxidation, whereas pyridoxine did not (Kannan *et al*, 2004). In a study comparing the ability of pyridoxine, pyridoxamine, pyridoxal and pyridoxal-5'-phosphate to prevent lipid glycation in an *in vitro* model, pyridoxal-5'-phosphate and pyridoxal performed significantly better than pyridoxine (Higuchi *et al*, 2006). Clinically, pyridoxal-5'-phosphate has been found to alleviate epileptic seizures which do not respond to treatment with pyridoxine (Kuo *et al*, 2002; Wang *et al*, 2005). In view of the foregoing, pyridoxal-5'-phosphate is distinct from pyridoxine.

Dosages of pyridoxine produce neurotoxicity when administered at the therapeutically effective amounts of claimed pyridoxine derivatives (Schaumberg et al., 1983, *N. Eng. Med. J.*; Bässler, 1988, *Internat. J. Vit. Nutr. Res.*; Holman, 1995, *J. Austral. Coll. Nutr. Environ. Med.*). In view of pyridoxine's neurotoxicity, the art as a whole teaches away from administering

pyridoxine at therapeutically effective amounts. "A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). If one was to extrapolate pyridoxine to pyridoxal-5'-phosphate and the other claimed compounds, one would also assume that a therapeutically effective dose would be toxic. However, pyridoxal-5'-phosphate has been therapeutically administered (both orally and parenterally) at dose levels up to 50 mg/kg/day to children with West syndrome and related disorders, with no treatment-related neurological findings or other major adverse findings reported (Hirai *et al*, 1998; Seki, 1990; Ohtsuka *et al*, 1987). Applicants respectfully assert that the prior art teaches away from a therapeutically effective does of pyridoxal-5'-phosphate, and the claimed subject matter is not obvious in view of the neurotoxicity teachings.

Nutritional vs. Therapeutic. Additionally, not all of the claim limitations (e.g., "a therapeutically effective amount") have been taught or suggested by the cited art. A nutritionally effective amount of vitamin B_6 is distinct from the disclosed therapeutically effective amounts of pyridoxal-5'-phosphate used to treat cerebral ischemia or ischemic stroke. (See table at S-12, "Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline".) In view of pyridoxine's neurotoxicity at therapeutically effective amounts, there is no teaching or suggestion of a therapeutically effective amount. The cited art only discusses pyridoxine at amounts to correct nutritional deficiencies. Since pyridoxine is toxic at higher dosages, there is not even a suggestion of therapeutically effective amounts of pyridoxine. Additionally, pyridoxine is not claimed and, as discussed above, is distinct from pyridoxal-5'-phosphate. Hence, the cited art does not teach nor suggest all of the instant claim limitations.

Additionally, more recent studies have demonstrated that pyridoxine does not prevent myocardial infarction or cerebral vascular accidents, nor does pyridoxine produce beneficial effects in subjects at high risk for cardiovascular events (Bønaa, 2006; HOPE2, 2006; Kolata, 2006). Applicants respectfully assert that the Examiner has not established a motivation to combine the cited art to arrive at the claimed subject matter or a reasonable expectation of success.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under § 103(a).

Co-pending and Related Applications

The Examiner requested a list of all co-pending and related applications (Office Action at page 2, second paragraph). Applicants have complied by filing a Form 1449 with an information disclosure statement. The Form 1449 lists co-pending and related applications.

Summary

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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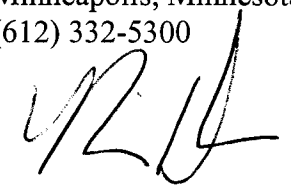

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